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Rifaximin for the prevention and treatment of hepatic encephalopathy: A systematic review with meta-analyses of randomised controlled trials

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Introduction:

The non-absorbable antibiotic rifaximin has been used to treat hepatic encephalopathy since the early 1980s. Its main licenced indication is for the prevention of a recurrence of HE although many early trials showed it was efficacious for the treatment of both acute and chronic HE. The aim of this systematic review was to assess the efficacy and safety of rifaximin in patients with cirrhosis by undertaking meta-analyses of RCTs comparing rifaximin vs. placebo/no intervention or vs. non-absorbable disaccharides (NADs)

Methods:

Extensive electronic and manual searches of the literature were undertaken; further information was obtained from trialists and pharmaceutical companies; ongoing trials were identified in ClinicalTrials.gov and similar trial registries. Meta-analyses were conducted and results presented as relative risks (RR) with 95% confidence intervals (CI). Subgroup and Trial Sequential Analyses were performed to evaluate sources of heterogeneity and the influence of random and systematic errors.

Results:

A total of 21 trials involving 2258 patients were included. Individual patient data were obtained for five trials and unpublished information from 10 trials. Rifaximin showed a beneficial effect on mortality compared with placebo/no intervention when including all 11 RCTs (RR 0.58, 0.44 to 0.77; participants=1129) and when including only the four RCTs with a low risk of bias (0.51, 0.31 to 0.84). Subgroup analyses showed that rifaximin reduced mortality in overt HE (0.50, 0.36 to 0.71), but not in minimal HE (0.50, 0.20 to 1.22), or in the prevention trials (1.01, 0.54 to 1.88) or when excluding the five RCTs in which NADs were used as co-intervention (0.74, 0.31 to 1.77) (Figure 1). Additional analyses showed a beneficial effect of rifaximin on overt HE (0.62, 0.41 to 0.93) and minimal HE (0.43, 0.30 to 0.62), but not in the prevention of HE (0.80, 0.45 to 1.42) or in an analysis that excluded RCTs in which NADs were used as co-invention (0.64, 0.39 to 1.04). Rifaximin reduced the risk of serious adverse events (SAE) (0.65, 0.51 to 0.84) and had a potential beneficial effect on Quality of Life (MD -2.05, -2.78 to -1.32). In meta-analyses of six RCTs comparing rifaximin vs. NADs, there was no effect on mortality (0.86, 0.42 to 1.77; participants=447). Rifaximin had a beneficial effect on overt HE (0.64, 0.43 to 0.93), but not minimal HE (0.85, 0.47 to 1.53) or in the prevention trials (0.89, 0.51 to 1.57); it did not reduce the risk of SAEs (RR 0.89, 0.56 to 1.42).

Conclusion:

There is moderate to low quality evidence that rifaximin combined with NADs is a safe and effective intervention for patients with cirrhosis and overt or minimal hepatic encephalopathy and for the prevention of recurrent hepatic encephalopathy after an index event.

Figure 1: Random-effects, meta-analysis of RCTs comparing the effect of rifaximin versus placebo/no intervention/lactulose on mortality in patients with cirrhosis